Fifth Annual Report 1996

Creutzfeldt-Jakob Disease Surveillance in the UK

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1

Summary

The national surveillance programme for CJD in the United Kingdom was initiated in May 1990. The information provided in this report continues to provide evidence of a high level of case ascertainment and that detailed clinical and epidemiological information has been obtained in the great majority of patients. A high post mortem rate has been maintained through the period of the study (1990-1996) The success of the project continues to depend on an extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the United Kingdom. We are particularly grateful to the relatives of patients for their help with the study.

Over a period of 25 years, the number of cases of CJD identified annually has increased. The major increase has been since 1990 and in 1994 the incidence of CJD was higher than in any previous year. It is impossible to say with certainty to what extent these changes reflect an improvement in case ascertainment and to what extent, if any, changes in incidence. Analysis demonstrates that the major reason for the increased incidence of cases is an increased number of cases of CJD in those aged 75 and over. It is of note however that the overall incidence figures for CJD in the United Kingdom are comparable to other countries in Europe and elsewhere in the world, including countries which are free of BSE.

There is no strong evidence of changes in the geographical distribution of CJD between the periods 1970-1994 (pre-BSE) and 1985-1995 (post-BSE). Previous analysis found no convincing evidence of space-time clustering during the earlier period and we have not found any convincing evidence of space-time clustering in the later period.

A case-control analysis of occupational histories has revealed no evidence that any of the occupations considered on biological grounds to be potentially at higher risk of CJD were actually associated with an increased risk of CJD. The occurrence of CJD in 4 farmers and 2 farmers' spouses is clearly a matter of concern. However, the incidence of CJD in farmers in continental Europe is similar to the UK and this does not suggest that there is any additional risk factor for CJD to farmers in the UK in relation to other countries.

Analysis of dietary histories has revealed statistical associations between various meats/animal products and risk of CJD. These apparent associations should be treated with great caution in view of the methodological problems of the case-control study including fragility of data and the possibility of recall bias. It is of note that the apparent dietary risk factors for CJD have varied from year to year and there is no consistent pattern.

The major finding since the last report has been the identification of a novel clinicopathological variant of CJD designated new variant CJD (nvCJD). The most plausible explanation for these cases is that they are causally linked to dietary exposure to the BSE agent, probably prior to the introduction of the specified bovine offal ban in 1989. The dietary case-control study of these cases has failed to reveal any convincing evidence of specific dietary risk factors but this does not refute the dietary hypothesis in view of the possibility of exposure to high titres of the BSE agent in a variety of food products, including those containing mechanically recovered meat. The retrospective identification of specific dietary risk factors may be impossible if such contamination was widespread and intermittent. The hypothesis of a causal link with BSE has been strengthened by evidence from transmission studies and protein subtype analysis but further evidence of a causal link may depend on animal transmission studies and continued epidemiological surveillance.

Section

2

Clinical Surveillance

Introduction

The national surveillance of Creutzfeldt-Jakob disease (CJD) was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (The Southwood Committee) and is funded by the Department of Health and the Scottish Home and Health Department. The primary aim of the project is to monitor CJD in order to identify any change in the pattern of this disease that might be attributable to the emergence of Bovine Spongiform Encephalopathy (BSE). This report documents the findings from the CJD Surveillance Project up to 30 April 1996.

Numbers of cases

In a series of studies, attempts have been made to identify all cases of CJD occurring in England and Wales since 1970 and in the UK since 1985. Methods of case ascertainment have been broadly similar throughout the period, based on referral by targetted professional groups and on death certificates. Cases of CJD in England and Wales during the period 1970-79 were identified retrospectively at the end of that period and a prospective surveillance system was instituted to detect cases during 1980-84. Prospective ascertainment of cases, extended to cover the whole of the UK, was re-instituted in May 1990 and is continuing. Cases in the UK for the period 1985-April 1990 were identified retrospectively.

Between 1st January 1970 and 30th April 1996, 682 cases of CJD were identified, 6 of them were alive at 30th April 1996. Of these, 521 (76%) were classified as definite cases and 161 as probable cases. Twenty-three iatrogenic cases and 17 inherited cases were identified and both of these groups have been excluded from analysis. Of the remaining 642 cases, 11 were of the recently described neuropathological variant. Numbers of cases of CJD are published monthly by the Department of Health and recent figures are appended (Appendix 1).

The numbers of deaths from CJD in each year since 1970 is shown for England and Wales in Figure 1a and for Scotland and Northern Ireland since 1985 in Figure 1b. In England and Wales, the numbers of deaths identified increased from about 10 per year at the beginning of the 1970s to about 35 per year in the 1990s. No increase in the annual number of cases is evident for Scotland and Northern Ireland since 1985.

Figure 2 shows average annual age- and sex-specific mortality rates over the study period. Below 40 years of age mortality rates were extremely low (< 0.1/million/year). They increased in the 50-59 year age group and reached a peak of around 2/million/year in the 60-69 year age group. Thereafter they declined in persons aged 70 years and above.

Table 1 shows numbers of deaths in 10-year age groups for each two-year period from 1970 to 1995 and cases identified up to 30th April 1996. Mortality rates over the period increased substantially in those aged 70 years or more and by successively smaller proportions in those aged 60-69 years and 50-59 years (Figure 3 and Table 2). The increase in those aged 40-49 years did not approach statistical significance (p=0.27). Under the age of 40 years the numbers of cases were small, but of the 7 cases dying aged less than 30 years, 6 had onset after 1st January 1994.

The number of deaths from definite and probable CJD (sporadic and nvCJD) by region and county from 1/5/90 to 30/4/96 are listed in Table 3. The geographical distribution of cases of CJD by place of residence at death for the period 1st May

Table 1 Cases of Creutzfeldt-Jakob Disease[1] in England and Wales (from 1970) and the U.K. (from 1985)

Age (years)	Year of death														Total
	70-71	72-73	74-75	76-77	78-79	80-81	82-83	84-85[2]	86-87	88-89	90-91	92-93	94-95	1996[3]	
10-19	0	0	0	0	0	1	0	0	0	0	0	0	1	1	**3**
20-29	0	0	0	0	0	0	0	0	0	0	0	0	1	3	**4**
30-39	1	0	0	2	2	1	1	4	1	0	1	0	1	3	**17**
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	3	**26**
50-59	7	9	11	6	11	13	12	10	5	13	18	12	14	3	**144**
60-69	9	13	10	22	17	24	20	28	22	17	28	38	31	6	**285**
70 +	2	2	2	4	9	4	12	16	18	17	9	28	37	3	**163**
Total	**21**	**24**	**25**	**35**	**40**	**45**	**46**	**58**	**49**	**49**	**58**	**81**	**89**	**22**	**642**

[1] Excludes cases known to be iatrogenic or inherited
[2] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included
[3] Up to 30 April 1996 only.

Table 2 Rate of increase in mortality from sporadic CJD by age group

Age group (years)	Average % increase over a two-year period	95% confidence interval	p-value
40-49	7%	-4.8%, 19.5%	0.27
50-59	4%	-0.1%, 8.8%	0.08
60-69	7%	3.9%, 10.8%	<0.001
70+	21%	15.4%, 27.5%	<0.001

TABLE 3 DEATHS FROM DEFINITE & PROBABLE SPORADIC CJD AND nvCJD BY REGION AND COUNTY: 1/1/90 - 30/4/96

	No of cases	Total no (incidence /annum)
ENGLAND		
North		
Cleveland	0	
Cumbria	5	
Durham	4	14 (0.75)
Northumberland	1	
Tyne & Wear	4	
East Midlands		
Derbyshire	1	
Leicestershire	5	
Lincolnshire	0	9 (0.37)
Northamptonshire	1	
Nottinghamshire	2	
South East		
Bedfordshire	4	
Berkshire	3	
Buckinghamshire	1	
East Sussex	2	
Essex	5	
Greater London	27	60 (0.56)
Hampshire	2	
Hertfordshire	0	
Isle of Wight	1	
Kent	5	
Oxfordshire	4	
Surrey	1	
West Sussex	5	
North West		
Cheshire	3	
Greater Manchester	10	28 (0.73)
Lancashire	7	
Merseyside	8	
WALES		
Clywd	0	
Dyfed	1	
Gwent	4	
Gwynedd	6	
Mid Glamorgan	2	
Powys	2	
South Glamorgan	2	
West Glamorgan	4	
TOTAL FOR WALES		**21 (1.20)**
NORTHERN IRELAND	2	**2 (0.20)**

	No of cases	Total no (incidence /annum)
ENGLAND		
Yorkshire & Humberside		
Humberside	2	
NorthYorkshire	5	
South Yorkshire	4	20 (0.66)
West Yorkshire	9	
East Anglia		
Cambridgeshire	1	
Norfolk	5	10 (0.79)
Suffolk	4	
South West		
Avon	6	
Cornwall	4	
Devon	8	
Dorset	7	35 (1.22)
Gloucestershire	3	
Somerset	3	
Wiltshire	4	
West Midlands		
Hereford & Worcs.	1	
Shropshire	1	
Staffordshire	2	14 (0.44)
Warwickshire	1	
West Mids (Met)	9	
TOTAL FOR ENGLAND		**190 (0.65)**
SCOTLAND		
Borders	0	
Central	1	
Dumfries & Galloway	0	
Fife	2	
Grampian	5	
Highland	1	
Lothian	4	
Strathclyde	11	
Tayside	1	
Islands	1	
TOTAL FOR SCOTLAND		**26 (0.84)**

1990 to 30th April 1996 is shown in Figure 7. The annual incidence of CJD ranged from 0.37 cases/million in the East Midlands to 1.22 cases/million in the South West.

The annual incidence rate of CJD (sporadic and nvCJD) in the period 1st May 1990 to 30th April 1996 was 0.65 cases/million in England, 1.2 cases/million in Wales, 0.84 cases/million in Scotland and 0.20 cases/million in Northern Ireland.

Data have also been analysed by regional health authority for hospital at diagnosis. Table 4 lists the deaths per annum of definite and probable cases together with the number of referrals by regional health authority.

Standardised mortality rates (SMRs) for the standard regions of England and Wales are shown in Figure 4 for the period 1970-1984 and for all of the UK in Figure 5 for the period 1985-April 1996. The highest SMR in the earlier period was in the South East and Wales while in the later period (including data from Scotland) the highest SMRs were found in the South West, Wales and Scotland. After adjusting for age and sex, there was not strong evidence that the geographical distribution of CJD changed between the two periods (p=0.08).

Comment

There has been an increase in the number of sporadic cases of CJD recorded in England and Wales over the period 1970-April 1996. During a period of prospective surveillance prior to the advent of BSE (1980-84) the annual incidence of sporadic CJD in England and Wales averaged 24.8 cases. During prospective surveillance following the BSE epidemic (1990-96) the annual incidence of sporadic CJD in England and Wales has averaged 34.5 cases. Substantial increases in the reported incidence of CJD have been observed in countries in which BSE is rare or absent and in which surveillance of CJD has been undertaken (Table 5).

TABLE 4 REGIONAL HEALTH AUTHORITIES FOR HOSPITAL AT DIAGNOSIS (ALL FORMS OF CJD)

	1990 (from 1 May)		1991		1992		1993		1994		1995	
	Referrals	Deaths	Referrals	Deaths	Referrals	Deaths	Referrals	Deaths	Referrals	Deaths	Referrals	Deaths
N.E. Thames	8	1	6	2	4	2	6	2	6	2	3	2
S.E. Thames	2	1	8	2	8	1	2	0	9	5	6	1
S.W. Thames	3	1	3	2	6	1	4	3	7	4	4	2
N.W. Thames	1	0	7	2	7	3	2	1	5	3	2	2
North Western	2	0	5	3	14	7	5	3	8	4	10	4
South Western	3	1	4	1	3	4	9	6	9	5	10	6
Northern	4	1	3	1	10	5	4	4	8	4	6	1
West Midlands	3	0	3	3	4	4	5	2	6	3	5	5
Yorkshire	3	2	6	3	4	1	5	3	6	2	2	1
Trent	3	2	3	1	5	2	6	3	3	2	3	2
Oxford	2	2	4	4	1	0	4	3	4	4	5	4
Wessex	2	0	2	2	3	2	4	3	7	2	6	5
East Anglian	2	2	1	0	4	3	2	2	5	4	3	1
Mersey	1	0	2	0	4	4	1	0	5	4	5	2
Special HA	2	1	4	3	2	1	3	1	2	2	2	1
Wales/Clywd	0	0	0	0	0	0	0	0	0	0	2	0
Wales/E Dyfed	0	0	0	0	1	1	0	0	0	0	0	0
Wales/M Glam	1	1	0	0	0	0	0	0	0	0	0	0
Wales/S Glam	0	0	0	0	4	2	2	1	1	1	1	0
Wales/W Glam	0	0	0	0	2	2	0	0	2	1	2	2
Wales/Gwynedd	0	0	2	2	0	0	1	0	2	1	1	0
Wales/Gwent	0	0	0	0	0	0	1	1	1	1	1	1
Wales/Powys	0	0	0	0	0	0	1	0	1	1	0	0
Scotland/Ayr & Arran	0	0	0	0	0	0	1	0	1	0	0	0
Scotland/Grampian	2	2	2	1	1	0	2	1	0	1	1	1
Scotland/G Glasgow	1	0	3	2	3	2	4	4	2	1	2	1
Scotland/Lanarkshire	0	0	1	1	0	0	0	0	0	0	1	1
Scotland/Borders	2	0	0	0	0	0	0	0	0	0	1	0
Scotland/Forth Valley	1	0	0	0	1	0	0	0	1	0	1	0
Scotland/Lothian	3	1	4	0	4	3	1	0	5	0	0	0
Scotland/Fife	0	0	0	0	0	0	2	2	1	0	0	0
Scotland/Tayside	0	0	1	1	0	0	0	0	7	1	0	0
Scotland/Highland	0	0	0	0	0	0	0	0	1	1	0	0
Northern Ireland	1	0	1	0	1	1	1	1	1	0	1	1
TOTAL	**52**	**18**	**75**	**36**	**96**	**51**	**78**	**46**	**116**	**59**	**86**	**46**

Such increases are most likely to reflect improved case ascertainment, rather than real increases in the incidence of disease. The age distribution of CJD in the UK (Figures 2 and 6) is similar to that observed in many countries, with a decline in the incidence in those aged above 70 years. It has long been suspected that the decline in incidence in older people is due to under-ascertainment of cases in the older age groups. In the UK the greatest increase in incidence has been in those aged over the age of 70 years, with smaller increases between ages 40 and 70 years (Figure 3). For many diseases case ascertainment is likely to be poorest among the old and best among the age groups in which death, from any cause, is an unusual occurrence. Thus, with the exception of the increased number of cases in the youngest age groups, the age-specific time trends suggest that improved ascertainment might be a reasonable explanation for much or all of the apparent rise in incidence of CJD since 1970.

Table 5 Incidence of CJD in countries other than the UK over time

Country	Period	Incidence/million/year
Chile	1955-72 1973-77 1978-83	0.10 0.31 0.69
France	1968-77 1978-82 1992-94	0.34 0.58 0.81
Germany	1979-90 1993-94	0.31 0.68
U.S.A.	1973-77 1986-88	0.26 0.83

Space-time clustering of CJD

The method of Knox was used to look for evidence of clustering of cases of CJD in space and time (which might provide evidence of case-to-case transmission or a

common source of infection). Three hundred and fifty-three cases in Great Britain, identified with onset on or after 1st January 1985, were included in the analyses. Cases known to be iatrogenic or familial were excluded, as was one case from the Shetland Islands. When known, date of clinical onset was used as the time point in the analyses. When date of onset was unknown (approximately 3% of cases), it was set at 4 months prior to the date of death (4 months being the median duration from onset to death for cases with known date of onset).

The results of the Knox analyses of these 353 cases are shown in Table 6.

Table 6 Space-time clustering of dates and places of onset of 353 cases of sporadic Creutzfeldt-Jakob disease in Great Britain, with onset between January 1985 and April 1996: observed and expected numbers of pairs of cases with onsets within "critical" time and space distances of each other

Time[1] between dates of onset	Distance between places of residence at onset							
	< 5km		< 10 km		< 20 km		< 50km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	7	6.7	11	11.3	29	28.6	77	79.7
1-3 months	12	10.1	20	17.1	38	43.2	107	120.7
3-6 months	16	15.3	28	26.1	67	65.8	202	183.6
6-12 months	22	29.8	45	50.7	130	127.8	342	356.7
1-2 years	49	53.1	86	90.3	216	227.7	589	635.6
2-3 years	45	45.2	70	76.9	200	194.0	566	541.4
3-4 years	52*	38.0	87**	64.6	177	163.0	462	455.0
4-5 years	37	31.8	60	54.0	134	136.2	341	380.1

[1] Critical times used were (in days): 35, 95, 185, 370, 735, 1100, 1465, 1830

* $0.01 < p \leq 0.05$

** $p \leq 0.01$

For most space-time combinations the observed number of pairs is close to the number expected under the null hypothesis (no space-time clustering). Only two cells had excesses of observed pairs statistically significant at the 5% level. In the most significant of these, 87 pairs were observed to occur within 10km of each other with onset 3 to 4 years apart (compared with about 65 such pairs expected, p=0.005). Forty-four of these observed pairs occurred in three "clusters". Two of these clusters were in the Greater London area (one of 16 cases forming 25 pairs

over the period 1986-1994, the other of 8 cases forming 9 pairs over the period1985-1996). The third "cluster" occurred in the Glasgow area (7 cases forming 10 pairs over the period 1987-1994).

An analysis of 543 out of 546 cases of sporadic CJD identified in England and Wales over the past 26 years (since 1970) is presented in Table 7. (The analysis is restricted to cases in England and Wales as during the period 1970 to 1984 only cases in England and Wales were recorded.)

Table 7 Space-time clustering of dates and places of onset of 543 cases of sporadic Creutzfeldt-Jakob disease in England and Wales, January 1970 to April 1996: observed and expected numbers of pairs of cases with onsets within "critical" time and space distances of each other

Time[1] between dates of onset	Distance between places of residence at onset							
	< 5 km		< 10 km		< 20 km		< 50 km	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
< 1 month	4	5.7	7	13.8	35	38.9	105	119.6
1-3 months	9	8.5	22	20.7	48	58.5	153	180.2
3-6 months	18	12.8	29	31.1	80	87.8	283	270.1
6-12 months	33*	24.3	65	59.0	196**	166.5	518	512.3
1-2 years	45	46.4	102	112.7	325	318.1	956	978.8
2-3 years	35	43.5	87	105.8	297	298.6	960	918.9
3-4 years	56**	39.6	101	96.3	275	271.9	855	836.6
4-5 years	46	37.3	91	90.7	233	255.9	780	787.6
5-6 years	42	36.2	94	87.9	262	248.2	778	763.9
6-7 years	31	34.3	81	81.3	235	235.1	745	723.5
7-8 years	41	33.7	90	81.8	250	231.0	743	710.9
8-9 years	33	30.7	70	74.5	201	210.4	653	647.6
9-10 years	23	32.2	68	78.3	227	221.1	711	680.4
10-15 years	91	115.8	265	281.4	747	794.5	2274	2444.8
15-20 years	50	61.4	188**	149.2	458	421.2	1298	1296.3

[1] Critical times used were (in days): 35, 95, 185, 370, 735, 1100, 1465, 1830, 2195, 2560, 2925, 3285, 3655, 5490, 7310

* $0.01 < p \leq 0.05$

** $p \leq 0.01$

Overall, there is little convincing evidence of space-time clustering of cases in these data. There was an excess of pairs of cases with onsets 3 - 12 months apart recorded as living within 5 km of each other (51 observed, 37.1 expected; p=0.02). Twenty of these observed pairs arose from 18 cases in the Greater London area forming "three" clusters (during the periods 1985-87, 1991 and 1993-94). There was also an excess of pairs of cases recorded as living within 5 km of each other with onsets 3 - 5 years apart (102 observed, 76.9 expected; p=0.004). A large "cluster" of 20 cases occurring in the Greater London area over the period 1981 to 1994 was responsible for 45 of these pairs. Excesses of pairs were also observed for cases with onset 6-12 months apart living within 20 km of each other (p=0.01), and cases with onset 15-20 years apart living within 10 km of each other (p=0.001) or within 20 km of each other (p=0.04).

Given the number of cells in the table (60), it is not surprising that several cells contain apparent excess pairs of cases which are "statistically significant" at the 5% level. That these excesses tend to include "clusters" of cases in Greater London may be artefactual, arising from the use of a central grid reference for some cases (when the precise place of residence was not recorded).

Section 3

Case-Control Study

In addition to the analysis of the epidemiology of CJD presented in Section 1, a case-control study of CJD has been carried out in the UK since May 1990. Relatives of patients with suspect CJD are interviewed using a standard questionnaire adapted from a previous study which includes a wide range of questions relating to putative risk factors of CJD including occupational history and dietary history. For each case, a control is identified who is a patient at the same hospital and is matched for sex and age $\pm$ 4 years. Cases with diseases which might be confused clinically with CJD are excluded. Where possible, a relative of the same degree is interviewed using the standard questionnaire and if this is not possible the control is interviewed directly. Since May 1990 a relative of the control has been interviewed on 56% of occasions and the control themselves has been interviewed on 44% of occasions.

Dietary history and the risk of CJD

In last year's annual report caveats relating to the dietary case-control study were stated in detail. In brief, the findings concerning dietary history are particularly difficult to interpret for a number of reasons:

1. the inevitably small number of cases included in the case-control study results in instability of data.
2. there is a potential misclassification of exposure as responses to the dietary case-control study are obtained from a relative rather than directly from the patient. It is known that accurate dietary histories are very difficult to obtain, even directly from

individuals about their own diet, particularly when information is required on eating habits many years previously.

3. there is a substantial potential for response bias as the relatives of cases are often aware of the dietary hypotheses being tested.

In the Second Annual Report (1993) pudding consumption appeared to be a major dietary risk factor for Creutzfeldt-Jakob disease but it is of note that in analyses in the subsequent two years no significant association between pudding eating and risk of CJD was observed. The major apparent dietary risk factor for CJD in the analysis in 1994 was veal consumption, but in the 1995 analysis veal did not appear to be a risk factor when account was taken of potential confounding variables. In last year's analysis when account was taken of potential confounding variables the only apparent remaining dietary risk factor for CJD was consumption of venison at least once per year.

The changes in apparent dietary risk factors for CJD from year to year underline the fragility of the apparent dietary associations, particularly in relation to relatively rare dietary exposures.

Results

One hundred and eighty-seven cases of classic, sporadic Creutzfeldt-Jakob disease identified between May 1990 and April 1996 (82%) were compared with age-, sex- and hospital-matched controls with regard to lifetime history of eating of a wide range of animal tissues and products. Consumption was recorded as follows: never, less than once per year, more than once per year but less than monthly, more than once per month but less than once per week, once per week or more, eaten but frequency unknown. For all cases and for 105 (56%) controls, information on dietary history was obtained from a relative. For the remaining 82 controls, information was obtained from the control themselves. In addition to collecting information on lifetime dietary history, dietary history since 1985 was also recorded for 175 (94%) of the case-control pairs for some specific animal tissues/products. The analyses were

performed using the computer package STATA and all estimates take account of the individual matching.

The results of the comparison of 187 case-control pairs with regard to lifetime consumption of different types of meat is shown in Table 8. Evidence of dose-response relationships was sought by fitting the consumption categories described above as a continuous variable and is indicated by the trend test shown in the table. For lamb, pork, beef, poultry and fish the category "never eaten" was excluded from these analyses of trend. For veal and venison the category "never eaten" was included in the analysis of trend, since its exclusion would have resulted in the loss of a large number of case-control pairs from the analysis. Thus, it should be noted that the two different p-values for veal and venison are **not** independent of each other.

Pork, poultry and fish were consumed by almost all cases and controls. There was no evidence that cases consumed these items more often than controls. Lamb and beef were also consumed by most, although more cases than controls were reported to have ever eaten lamb (p=0.08). Cases were reported to consume beef more often than controls (trend: p=0.02). Among individuals reported to have eaten lamb there was no evidence that cases ate it more often than controls.

Consumption of venison and veal was much less common among both cases and controls than was the consumption of other meats. For both of these meats there was evidence that increasing frequency of reported consumption was associated with increased risk of CJD (test for trend; venison, p = 0.007; veal, p = 0.006).

Table 8 Results of a comparison between 187 cases of classic, sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls with regard to lifetime history of eating different types of meat

Type of meat	Cons-umed	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (OR=1)	p-value[1] (trend)
Lamb	No	2 (1)	8 (4)	1.0	-	0.08	0.22
	Yes	184 (99)	177 (96)	4.00	(0.85,18.8)		
Pork	No	0 (0)	2 (1)	1.0	-	0.50	0.62
	Yes	186(100)	183 (99)	∞	(0.19,∞)		
Beef	No	0 (0)	1 (1)	1.0	-	1.00	0.02
	Yes	186(100)	184 (99)	∞	(0.03,∞)		
Venison	No	124 (68)	147 (79)	1.0	-		0.007[2]
	Yes	59 (32)	40 (21)	1.79	(1.09,2.95)		
Veal	No	113 (62)	131 (72)	1.0	-		0.006[2]
	Yes	70 (38)	52 (28)	1.62	(0.99,2.63)		
Poultry	No	0 (0)	0 (0)	-	-	-.	0.53
	Yes	184(100)	185(100)	-	-		
Fish	No	1 (1)	0 (0)	1.0	-	1.00	0.55
	Yes	184 (99)	183(100)	0.00	(0.00,39.0)		

In order to investigate further the associations observed (for lamb, beef, venison and veal), the consumption data were regrouped into the following categories:

- lamb and beef; less than monthly, at least monthly, weekly;
- venison and veal; never, less than yearly, yearly.

[1] For lamb, pork, beef, poultry and fish the test for tend excludes the category "never eaten". For venison and veal the category "never eaten" is included in the analysis.

[2] See comment in text.

(Regrouping was performed because with the original five categories used the data were sparse in some categories).

Table 9 presents the results of an analysis of these data. There is evidence that the risk of CJD increases with the reported frequency of consumption of beef (p=0.007), venison (p=0.003) and veal (p=0.01). For beef there is an approximately three-fold increase in risk associated with eating beef every week compared with eating it less than once per month. The evidence for an association between reported consumption of lamb is weak (p=0.14), although individuals consuming lamb on a monthly basis appear to be at increased risk compared with individuals eating lamb less often than that (odds ratio =2.03; 95% c.i. 1.21, 3.42). When the analysis is restricted to only those case-control pairs in which a relative of the control was interviewed the overall pattern of the results remains largely unchanged (Table 10).

Table 9 Results of an analysis of trends in consumption of lamb, beef, venison and veal between cases of classic, sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (trend)
Lamb	< monthly	40 (22)	62 (34)	1.0	-	
	monthly	108 (59)	86 (47)	2.03	(1.21,3.42)	0.14
	weekly	36 (20)	36 (20)	1.42	(0.79,2.56)	
Beef	< monthly	14 (8)	30 (16)	1.0	-	
	monthly	79 (43)	82 (44)	2.16	(1.04,4.50)	0.007
	weekly	91 (49)	73 (39)	2.81	(1.34,5.89)	
Venison	never	124 (68)	147 (79)	1.0	-	
	< yearly	42 (23)	37 (20)	1.32	(0.77,2.27)	0.003
	yearly	16 (9)	3 (2)	7.91	(1.80,34.8)	
Veal	never	113 (62)	131 (72)	1.0	-	
	< yearly	42 (23)	39 (21)	1.16	(0.65,2.09)	0.01
	yearly	28 (15)	13 (7)	2.95	(1.31,6.63)	

Table 10 Results of an analysis of trends in consumption of lamb, beef, venison and veal comparing cases of classic, sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls, for those 105 pairs with data obtained from relatives.

Type of meat	Frequency of consumption	Odds ratio	95% confidence interval
Lamb	< monthly	1.0	
	monthly	1.72	(0.86,3.43)
	weekly	1.33	(0.60,2.94)
Beef	< monthly	1.0	
	monthly	2.49	(0.85,7.31)
	weekly	3.43	(1.20,9.84)
Venison	never	1.0	
	< yearly	1.58	(0.77,3.26)
	yearly	∞	(1.18,∞)
Veal	never	1.0	
	< yearly	1.29	(0.53,3.15)
	yearly	1.76	(0.69,4.50)

In addition to data on frequency of eating different types of meat, data were also collected on frequency of eating other animal tissues or products. Table 11 presents a comparison of cases and controls with regard to lifetime consumption of other products investigated. Only one case and one control were reported to have ever eaten eyes.

Almost all cases and controls were reported to have eaten sausages at some time and there was no evidence of any dose-response relationship. Similar proportions of cases and controls were reported to have eaten tripe, liver, trotters, puddings and heart (odds ratios all less than 1.25), with no evidence of a dose-response relationship for any of these items. More cases than controls were reported to have eaten tongue and haggis (odds ratios of about 1.5), but these differences were not statistically significant, nor was there any evidence of a dose-response relationship. More cases than controls were reported to have eaten kidney, sweetbreads and

brain (odds ratios of 1.61, 2.00 and 3.28 respectively; p = 0.05, 0.05 and 0.002 respectively).

Table 11 Results of a comparison between 187 cases of classic sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls with regard to lifetime history of eating various animal products

Type of product	Cons-umed	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (OR=1)	p-value[2] (trend)
Sausage	No	2 (1)	3 (2)	1.0	-	1.00	0.83
	Yes	181 (99)	181 (97)	1.50	(0.25,8.98)		
Tripe	No	117 (64)	121 (67)	1.0	-	0.40	(0.37)
	Yes	67 (36)	60 (33)	1.23	(0.76,1.97)		
Liver	No	18 (10)	19 (10)	1.0	-	0.72	(0.76)
	Yes	168 (90)	164 (90)	1.13	(0.57,2.27)		
Kidney	No	52 (28)	69 (38)	1.0	-	0.05	(0.30)
	Yes	132 (72)	114 (62)	1.61	(1.00,2.58)		
Sweet-breads	No	153 (85)	166 (91)	1.0	-	0.05	(0.03)
	Yes	26 (15)	16 (9)	2.00	(1.00,4.00)		
Tongue	No	68 (38)	80 (43)	1.0	-	0.18	(0.79)
	Yes	112 (62)	104 (57)	1.43	(0.84,2.44)		
Brain	No	153 (85)	176 (95)	1.0	-	0.002	(0.009)
	Yes	26 (15)	10 (5)	3.28	(1.41,7.65)		
Trotters	No	134 (74)	132 (73)	1.0	-	0.80	(0.81)
	Yes	46 (26)	50 (27)	0.94	(0.57,1.54)		
Puddings	No	75 (41)	79 (43)	1.0	-	0.25	(0.43)
	Yes	107 (59)	104 (57)	1.06	(0.65,1.74)		
Haggis	No	113 (62)	130 (70)	1.0	-	0.07	(0.16)
	Yes	69 (38)	55 (30)	1.58	(0.96,2.58)		
Heart	No	117 (65)	122 (68)	1.0	-	0.47	(0.46)
	Yes	64 (35)	58 (32)	1.18	(0.74,1.90)		

[2] For sausage the test for trend excludes the category "never eaten". For all other items the category "never eaten" is included in the analysis of trend, and the two p-values are not independent of each other.

Table 12 presents a more detailed analysis of the associations between lifetime consumption of kidneys, sweetbreads and brains, and risk of CJD, with consumption regrouped into 3 categories: never; less than once per year; once per year or more.

Table 12 Results of analysis of trends in lifetime consumption of kidneys, sweetbreads and brains between cases of classic sporadic Creutzfeldt-Jakob disease, post April 1990, and their matched controls

Type of meat	Frequency of consumption	Number of cases (%)	Number of controls (%)	Odds ratio	95% c.i.	p-value (trend)
Kidneys	never	52 (29)	69 (39)	1.0	-	0.07
	< yearly	30 (17)	24 (13)	1.83	(0.94,3.59)	
	yearly	97 (54)	85 (48)	1.62	(0.98,2.67)	
Sweet-breads	never	153 (85)	166 (92)	1.0	-	0.04
	< yearly	18 (10)	12 (7)	1.78	(0.79,4.02)	
	yearly	8 (4)	3 (2)	2.67	(0.71,10.05)	
Brains	never	153 (86)	176 (95)	1.0	-	0.005
	< yearly	18 (10)	8 (4)	2.88	(1.11,7.47)	
	yearly	7 (4)	2 (1)	4.05	(0.82,20.06)	

Eating sweetbreads and brains were both associated with statistically significant trends, eating of these items once per year or more being associated with about a 2½- and 4-fold increases respectively in risk. The evidence for an association between the eating of kidneys and risk of CJD was more equivocal. There was no clear trend in the estimates of the odds ratios, nor was there strong statistical evidence of a trend ($p = 0.07$). Restricting attention to the subset of case-control pairs with exposure data obtained from relatives resulted in slightly stronger associations between consumption of both kidney and sweetbreads and risk of CJD and a slightly weakened association between consumption of brain and risk of CJD (data not shown).

Data on consumption, post-1985, of the animal tissues and products included in Table 11 were available for 175 case-control pairs. (Data on meat consumption post-1985 were not collected for some case-control pairs.) There was no statistical

evidence of an association between consumption since 1985 of any of the animal products listed in Table 11 and risk of CJD ($p > 0.10$ for all products). Twelve cases compared with 6 controls were reported to have eaten sweetbreads during this period (odds ratio = 2.2 [0.8,6.3]), 4 cases and 3 controls were reported to have eaten brains (odds ratio = 1.3 [0.3,6.0]) and 106 cases compared with 92 controls were reported to have eaten kidneys (odds ratio = 1.3 [0.8,2.0]).

It is likely that many of the dietary exposures considered are associated in the population. For example, individuals who eat a particular type of offal may be more likely to eat other types than individuals who do not. Thus there is potential for confounding of associations between dietary exposure and risk of CJD. In order to overcome this problem we modelled simultaneously the association between the different exposures identified above and risk of CJD. Thus a model including seven different items (lamb, beef, venison, veal, kidneys, sweetbreads, brains) was fitted. Each of these items was included as a variable with 3 levels of frequency (see Tables 9 and 12 above). In this model only two items showed evidence of independent dose-response relationships with risk of CJD; beef ($p = 0.02$) and brain ($p = 0.04$). Monthly consumption of beef was associated with an almost 3-fold increase in risk of CJD while weekly consumption was associated with a 3.3-fold increase. For brains the increase in risk almost 3-fold for irregular consumption (< yearly) and 3.6-fold for more regular consumption (Table 13).

Table 13 Results of analysis of trends in lifetime consumption of beef and brains between 187 cases of classic sporadic Creutzfeldt-Jakob disease, post April 1990, and their age- and sex-matched controls

Type of meat	Frequency of consumption	Odds ratio[3]	95% c.i.	p-value (trend)
Beef	< monthly	1.0	-	
	monthly	2.86	(1.15,7.12)	0.02
	weekly	3.31	(1.29,8.47)	
Brain	never	1.0	-	
	< yearly	2.98	(0.89,9.97)	0.04
	yearly	3.60	(0.60,21.48)	

[3] Estimates of the odds ratio adjusted for lamb, venison, veal, kidney and sweetbread consumption.

Table 14 presents a comparison of 187 CJD cases and 58 cases in which the suspect diagnosis of CJD was not subsequently confirmed with regard to the reported consumption of beef and brains. There is no evidence of a dose-response relationship between beef or brain consumption and risk of CJD. This finding suggests that the association observed when cases were compared with their matched, non-suspect controls may be due to recall bias. However, while the association between increased frequency of brain consumption and risk of CJD is not statistically significant, we cannot rule out the possibility that an important association exists.

Table 14 Results of analysis of trends in lifetime consumption of beef and brains between 187 cases of classic sporadic Creutzfeldt-Jakob disease, post April 1990, and 58 "non-cases"

Type of meat	Frequency of consumption	Number of cases (%)	Number of "non-cases" (%)	Odds ratio[4]	95% c.i.	p-value (trend)
Beef	< monthly	14 (8)	2 (4)	1.0		
	monthly	79 (43)	24 (42)	0.52	(0.11,2.50)	0.40
	weekly	91 (49)	31 (54)	0.47	(0.10,2.21)	
Brain	never	153 (86)	52 (90)	1.0		
	< yearly	18 (10)	4 (7)	1.56	(0.50,4.83)	0.56
	yearly	7 (4)	2 (3)	1.15	(0.23,5.75)	

[4] Based on an "unmatched" analysis.

In summary, the dietary case-control study has demonstrated statistical associations between the risk of CJD and the lifetime history of consumption of a number of food products, from a number of different animal species. These apparent associations should be viewed with great caution in view of the methodological problems with the case-control study including fragility of data and the possibility of recall bias. Analysis of the dietary case-control study in individuals identified as possible cases of CJD and in whom the diagnosis was subsequently not confirmed, continues to provide circumstantial evidence of recall bias.

Occupational history

The occupational history of cases, controls, their spouses and their parents have been analysed to identify employment in the following areas: medical/nursing/dentistry and related professions, laboratory work involving animals; work in pharmaceutical laboratories; work in other research laboratories; livestock farming/veterinary medicine; work in abattoirs/butchers' shops or other direct contact with animal carcasses; other occupations involving contact with animal products (eg leatherworkers).

There was no evidence that cases were more likely than controls to have ever worked in any of the above categories (Table 15). Twenty cases compared with 21 controls had worked in the medical professions; 11 cases compared with 17 controls had worked on farms/in veterinary medicine; 6 cases compared with 9 controls had worked in abattoirs/butchers' shops. (For an analysis of cases working in farming at the time of disease onset see below). One case had worked in an animal laboratory and two cases had worked in a pharmaceutical laboratory (all pre-1985). No other cases nor controls had ever worked in animal, pharmaceutical or other research laboratories. Slightly more cases than controls had worked in other occupations involving contact with animal products (17 versus 12; odds ratio = 1.56; p = 0.30)

Most cases (179) and controls (181) had been married at some point in their lives. There was no evidence that cases were more likely than controls to have had spouses who worked in the medical professions (6 cases, 10 controls) or farming (4 cases and 5 controls). No cases or controls had spouses who had worked in animal laboratories. One control had a spouse who had worked in a pharmaceutical laboratory while one case and one control had spouses who had worked in research laboratories. Seven cases compared with two controls had spouses who had worked in abattoirs/butchers' shops (odds ratio = 6.0, p = 0.12) while 6 cases compared with 2 controls had spouses who had worked in other occupations involving contact with animal products (odds ratio = 3.0, p = 0.29).

Table 15 Results of a comparison of 187 cases of classic sporadic CJD with their matched controls with regard to their lifetime occupational history and that of their spouse

Occupation	Exposure	Number(%) of cases	Number (%) of controls
Medical/paramedical /nursing/dentistry	Subject	20 (11)	21 (11)
	Spouse	6 (3)	10 (5)
Animal laboratory	Subject	1 (1)	0 (0)
	Spouse	0 (0)	0 (0)
Farmer/vet	Subject	11 (6)	17 (9)
	Spouse	4 (2)	5 (3)
Butcher/abattoir worker/other occupation with direct contact with animals/ carcasses	Subject	6 (3)	9 (5)
	Spouse	7 (4)	2 (1)
Occupation involving animal products	Subject	17 (9)	12 (6)
	Spouse	6 (3)	2 (1)

Similar patterns were observed with regard to the occupations of parents of cases and controls. Only one case had a parent who had worked in a laboratory (research). Excluding cases and controls who worked themselves or whose spouse worked in the medical profession, three cases and 4 controls had parents who had worked in the medical professions while 7 cases and 9 controls had parents who had worked in farming/veterinary medicine. Five cases compared with 3 controls had parents who had worked in abattoirs/butchers' shops while 5 cases and one control had parents who had worked in other occupations involving contact with animal products.

Analysis of specific occupations at the time of disease onset in classic sporadic CJD

Six cases of sporadic CJD (5 definite, 4 male), have been identified since 1st May 1990 in individuals whose occupation at disease onset was in one of the groups identified above (four were farmers and two the spouses of farmers). Case reports have been published for four of these. The ages at death of the cases were; 54, 54, 59, 61, 64 and 64 years. The five cases for whom neuropathology was performed all showed changes typical of CJD. None showed the "florid" plaques characteristic of nvCJD. The sixth, probable case followed a clinical course typical of sporadic CJD with characteristic EEG features.

Four of the six individuals lived or worked on dairy farms (on 3 of which there had been confirmed cases of BSE) and the other two lived or worked on farms with beef suckler herds (1 with a confirmed case of BSE). Two of the six cases were farmer's spouses. All had lived or worked on farms throughout their working lives. The distribution of these cases by occupational group is shown in Table 16.

There is a statistically significant excess of cases among animal farm workers (6 observed, 2.4 expected, P=0.03). All of these cases were cattle farmers, 4 of whom worked on farms with a case of BSE. This excess of cases is highly significant (4 observed, 0.58 expected, P=0.003). Two of the cases among farmers were on farms without a case of BSE compared to an expected number of 1.78 (p=0.5).

Table 16 Numbers of individuals, expected and observed cases of CJD in occupational groups at potential increased risk of infection with BSE.

Occupational group	Number of individuals in group[1]	Expected number of cases of CJD, 1/5/90 to 31/12/96	Observed number of cases of CJD, 1/5/90 to 31/12/96	Incidence /million/year	p-value[2]
Farm workers on farms with cattle, pigs, poultry, sheep or goats	447,162	2.36	6	2.01	0.03
Farm workers on farms with cattle (dairy or beef)	354,242	1.87	6	2.54	0.01
Farm workers on farms with dairy cattle	149,436	0.79	4	4.02	0.01
Farm workers on farms with a confirmed case of BSE	109,643	0.58	4	5.47	0.003
Veterinarians	8,225	0.03	0	0	1.0
Abattoir workers/ butchers/meat cutters	68,300[3]	0.15	0	0	1.0

[1] Numbers given for farm workers include spouses and represent an average over the period.
[2] p-values indicate the probability of obtaining the observed number of cases or more under the null hypothesis that there is no occupational risk of CJD
[3] includes an estimated 48,300 butchers/meat cutters in GB (1991 census), 12,400 staff involved in red meat slaughtering (MAFF) and 7600 staff involved in slaughtering of animals and production of meat in Northern Ireland (Department of Economic Development, Belfast).

There is a highly statistically significant excess of CJD cases among workers on dairy farms and farms with a confirmed case of BSE. However, the incidence of CJD in dairy farmers in the UK, while higher than in the general population in the UK, does not appear remarkable when compared with the incidence of CJD among dairy farmers in other European countries (see previous report). As the BSE epidemic has been largely confined to the UK, these findings suggest that dairy farmers may be at an increased risk of CJD for reasons other than exposure to the BSE agent. Also, a possible explanation for at least some of the apparent excess risk may be that case ascertainment of CJD for farmers in the UK has been better than in other occupations because of awareness of the possibility of a link between BSE and CJD. It should also be noted that, while some farm workers appear to be at increased risk of CJD compared with the general population, their absolute risk remains very low, with an annual incidence below 6/million/year.

Section 4

New variant CJD

In the last report reference was made to the identification of an individual aged 19 years with Creutzfeldt-Jakob disease and the conclusion of the report stressed the importance of continuing careful surveillance of CJD with particular reference to cases occurring at a young age.

Through the surveillance system, a number of young patients with CJD were identified in late 1995 and early 1996 with unusual clinical features including a prolonged duration of illness with prominent early psychiatric symptoms. Neuropathological examination in all cases demonstrated an unusual appearance with extensive florid plaque formation which had not previously been identified in the large series of patients examined neuropathologically at the Surveillance Unit. By March 1996, ten individuals showing this apparently novel clinicopathological phenotype had been identified and investigation had failed to reveal any plausible explanation for these cases. In particular sequencing of the open reading frame of the prion protein gene was normal with no evidence of any of the known mutations associated with hereditary forms of human prion disease. Crucially, no similar case had been identified in countries participating in parallel surveillance of CJD in the European Union including France, Germany, Italy and the Netherlands. The primary remit of the CJD Surveillance Unit has been to identify any change in the characteristics of CJD following the occurrence of bovine spongiform encephalopathy in the UK cattle population. The occurrence of a novel clinicopathological variant of CJD in the UK raised the possibility that there might be a causal link between BSE and the novel variant of CJD. On April 6th 1996 a paper describing the cases was published in the Lancet [Will RG, Ironside JW, Zeidler M,

Cousens SN, Estibeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996; 347: 921-925] and the paper concluded that perhaps the most plausible explanation for these cases was exposure to the BSE agent. (Since March 1996, 5 further pathologically confirmed cases of new variant CJD have been identified in the UK and one in France. The clinicopathological features of these cases are all consistent with the original published descriptions. A further case of "probable" new variant CJD has been identified recently in the UK and this case has been included in further analysis although criteria for the classification of "probable" new variant CJD cannot yet be fully validated. The dates of onset, referral, death and confirmation of diagnosis (if available) are shown in Figure 8).

The following analyses are based on 16 cases of nvCJD in the UK and include data obtained after April 1996.

Genetic analysis is available in 14 out of 16 UK cases of new variant CJD. None show mutations of the PrP gene and all patients have been methionine homozygotes at codon129 of the PRP gene.

Details of past medical history have been collected in all cases. No case has a history of neurosurgery or exposure to human pituitary derived hormones. Four new variant cases have a history of surgery after 1980 in comparison with three of the age- and sex-matched controls.

Dietary history and new variant CJD

These analyses are based on data from 16 cases of new variant CJD and their age- and sex-matched hospital controls. The reported consumption of various different meats by cases and controls is shown in Table 17.

Table 17 Results of a comparison between 16 cases of new variant Creutzfeldt-Jakob disease and 16 controls with regard to consumption of different types of meat

	Ever		Post 1985	
	Number of cases (N=16)	Number of controls (N=16)	Number of cases (N=16)	Number of controls (N=16)
Lamb	16	15	15	13
Pork	15	16	15	15
Beef	16	16	16	15
Venison	6	3	3	3
Veal	3	6	2	6
Poultry	16	16	16	15
Fish	16	16	14	15

Almost all cases and controls had eaten beef, poultry, lamb and fish since 1985. Three cases and three controls were reported to have eaten venison since 1985, while two cases and six controls had eaten veal. There was some evidence that cases consumed beef ($p=0.07$) and poultry ($p=0.08$) more frequently than the controls (Table 18). There was no evidence that cases consumed lamb, pork or fish more frequently than controls ($p > 0.2$).

Table 18 **Frequency of consumption, since 1985, of beef and poultry by 16 cases of nvCJD and their controls**

Type of meat	Frequency of consumption	Number of cases (n=16)	Number of controls (n=16)
Beef	< monthly	1	6
	monthly	3	5
	weekly	12	5
Poultry	< monthly	0	3
	monthly	3	5
	weekly	13	8

The observation that nvCJD cases are reported to have consumed beef more frequently than controls must be interpreted with great caution given the potential for recall bias (see discussion in Section 2).

All cases and controls had eaten sausages since 1985 (Table 19) and most had eaten liver, burgers, meat pies and puddings. About half were reported to have eaten kidneys. Only a small number of cases and controls were reported to have eaten haggis, heart, faggots, tongue, trotters or tripe since 1985. No cases or controls were reported to have ever eaten sweetbreads or eyes (Table 19), while only one control was reported to have tried "a spoonful" of brains on one occasion, in Italy in the mid 1980s. There were no striking differences between the proportions of cases and controls eating any of these items.

Among those eating sausages, liver, kidneys, puddings, burgers or pies since 1985, there was no evidence that cases ate these items more frequently than controls ($p > 0.3$) for all items, Wilcoxon rank-sum test).

Table 19 Results of a comparison between 16 cases of new variant Creutzfeldt-Jakob disease and 16 controls with regard to consumption of various animal "products"

	Ever		Post 1985	
	Number of cases (N=16)	Number of controls (N=16)	Number of cases (N=16)	Number of controls (N=16)
Sausages	16	16	16	16
Tripe	2	2	0	1
Liver	12	14	10	13
Kidney	8	9	7	8
Sweetbreads	0	0	0	0
Tongue	6	3	3	2
Brain	0	1	0	0
Trotters	3	0	1	0
Puddings	11	12	10	9
Eyes	0	0	0	0
Haggis	9	7	6	6
Heart	4	1	3	1
Burgers	13 (/13)	13 (/14)	13 (/13)	12 (/14)
Meat pies	7 (/7)	9 (/11)	7 (/7)	9 (/11)
Faggots	5 (/11)	5 (/11)	3 (/11)	3 (/10)

Occupation and new variant CJD

Table 20 presents a list of occupations for these cases and controls. No occupation stands out as unusually common among the cases.

Table 20 List of lifetime occupations for 16 cases of new variant Creutzfeldt-Jakob disease and 16 controls

Cases	Controls
Clerical worker (x 3)	Clerical worker (x 4)
Catering worker (x3)	Catering worker (x 2)
Engineering (x 2)	Engineering (x 2)
Shop assistant (x 2)	Shop assistant (x 4)
Hairdresser	Hairdresser (x 2)
Factory worker	Factory worker (x 2)
Stable hand	Management
Solicitor	Bar worker
Debt collector	Miner
Bar worker	Fireman
Nurse	Fairground worker
Laundrette worker	Road layer
Cable layer	Bottling
Forestry worker	Chicken factory worker
Chef	

Comment

The possibility of a causal link between BSE and new variant CJD was raised by the identification of a novel clinicopathological variant of Creutzfeldt-Jakob disease occurring in the UK. Since March 1996, 5 further cases of new variant CJD have been identified in the UK with clinical and pathological features consistent with the original description. The one case of new variant CJD reported in a 26-year old in France does not compromise the plausibility of this link since France has been one of the biggest markets for exported British beef, beef products and cattle. No other case of new variant CJD has been identified since March 1996 in any country outside the UK including those participating in the co-ordinated surveillance of CJD in the European Union.

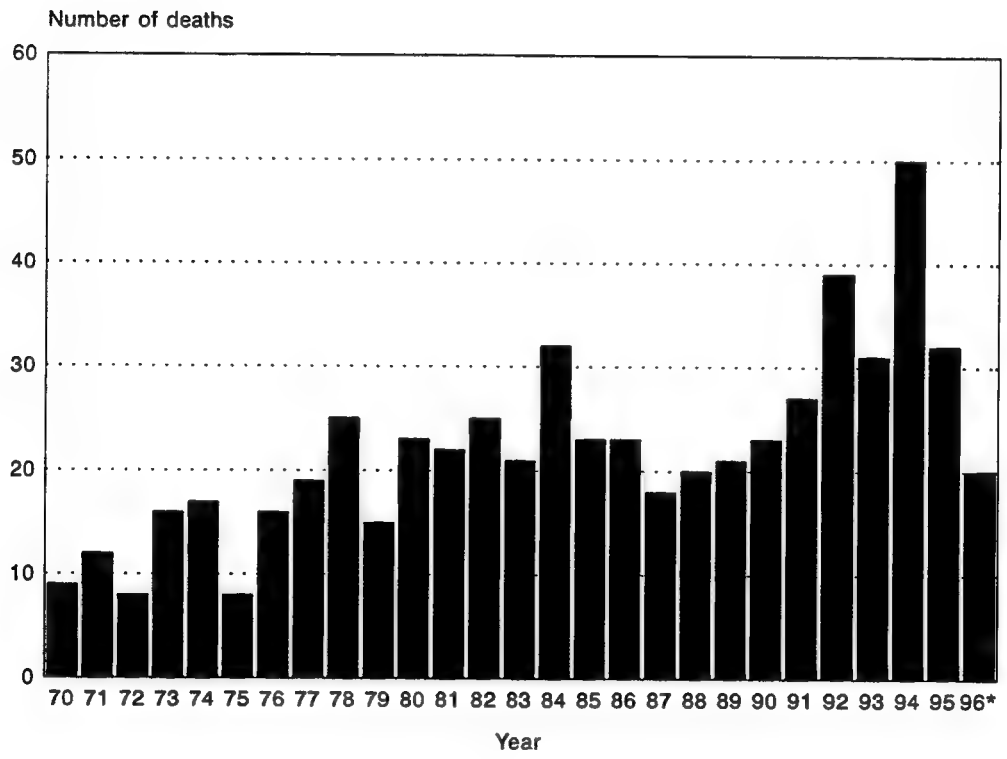
Extensive neuropathological case review has taken place in the UK and in many other countries and no other case of new variant CJD has been identified providing supportive evidence that new variant CJD is indeed a novel condition. Further evidence in support of the hypothesis of a causal link has been provided by the identification of similar neuropathological appearances in macaque monkeys inoculated with BSE and from analysis of the glycosylation pattern of prion protein subtypes. Strengthening the evidence for a causal link may depend on laboratory transmission studies and continued epidemiological surveillance.

Section 5

Figures and Appendix

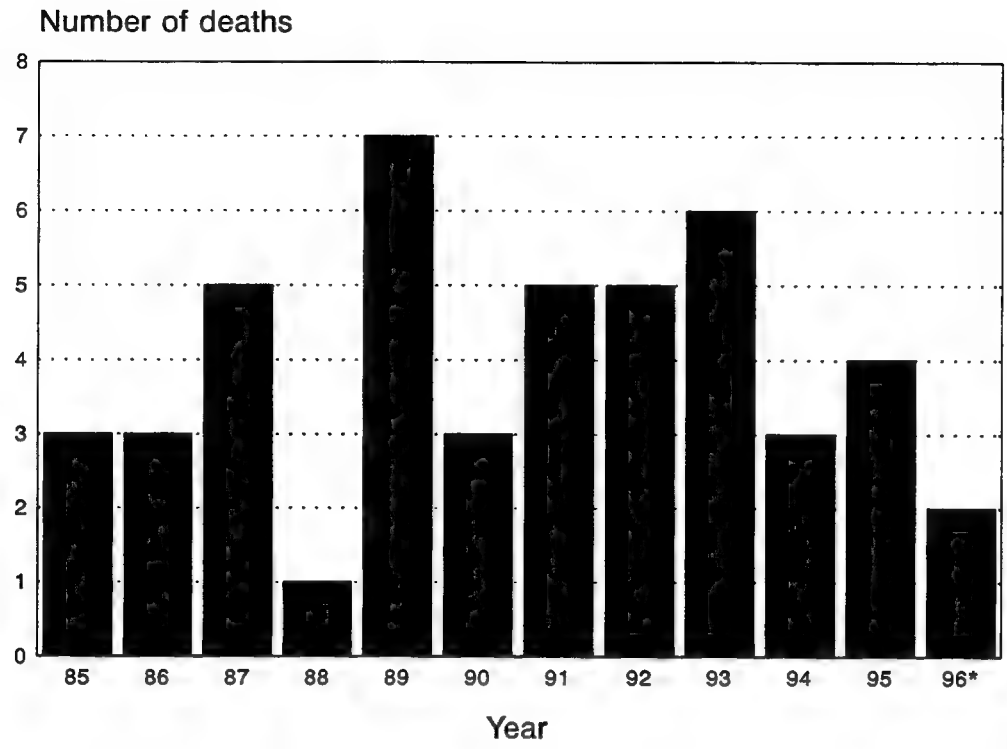
Figure 1a	Sporadic CJD and nvCJD deaths, England and Wales, 1970- April 96
Figure 1b	Sporadic CJD and nvCJD deaths, Scotland and Northern Ireland, 1985- April 1996
Figure 2	Age- and sex-specific mortality rates, 1970-1996
Figure 3	Mortality trends by age group
Figure 4	Standardised mortality ratios for sporadic CJD, England and Wales, 1970-84
Figure 5	Standardised mortality ratios for sporadic CJD, Great Britain, 1985- April 1996
Figure 6	Age-specific incidence rates for age at death
Figure 7	Geographical distribution of cases of CJD for period 1st May 1990 to 30th April 1996
Figure 8	Dates of onset, death, referral and confirmation of diagnosis for 14 cases of new-variant CJD in the UK

FIGURE 1a SPORADIC CJD AND nvCJD DEATHS
ENGLAND AND WALES, 1970- APRIL 1996



*Part year only

FIGURE 1b SPORADIC CJD AND nvCJD DEATHS
SCOTLAND AND NORTHERN IRELAND, 1985- APRIL 1996



*Part year only.

FIGURE 2 AGE- AND SEX-SPECIFIC MORTALITY RATES, 1970-1996

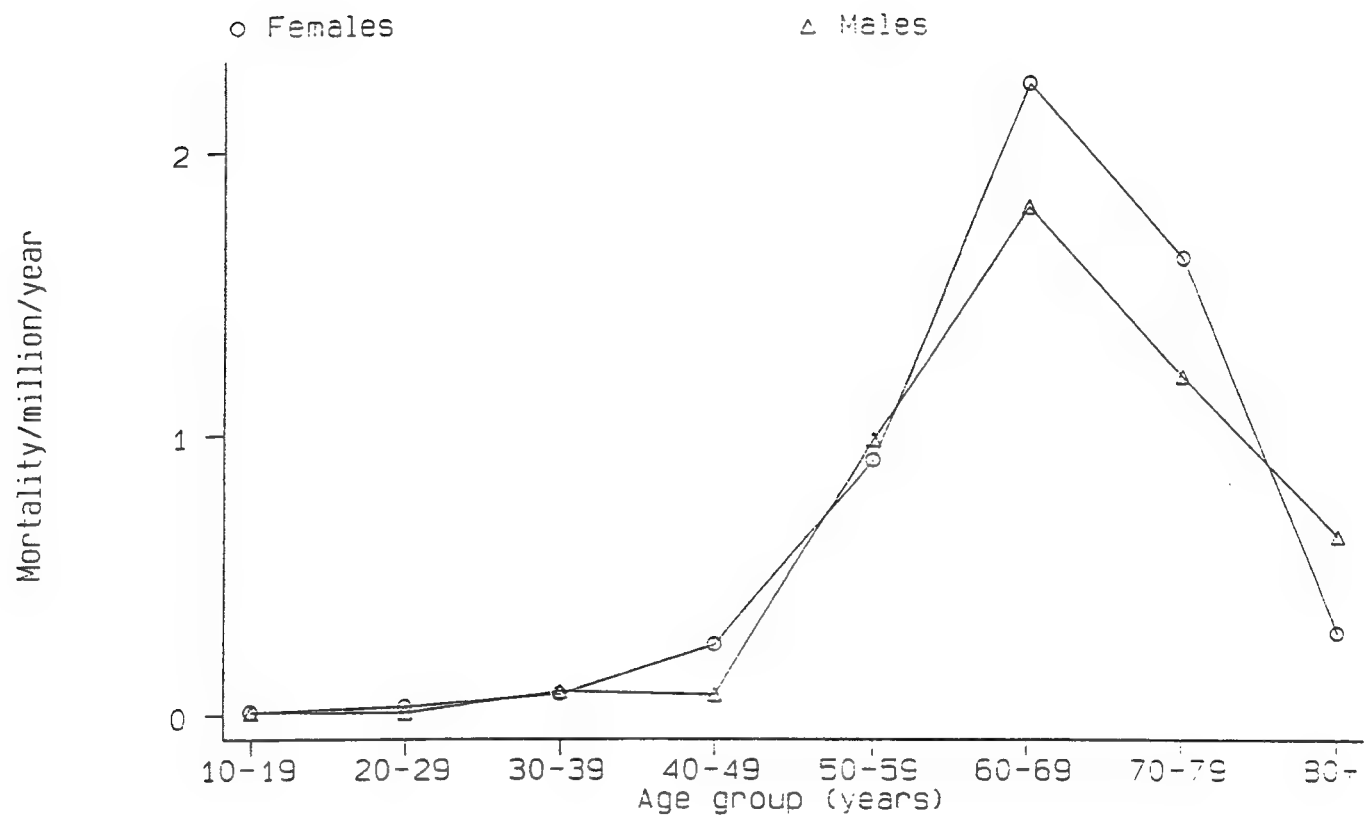


FIGURE 3 MORTALITY TRENDS BY AGE GROUP

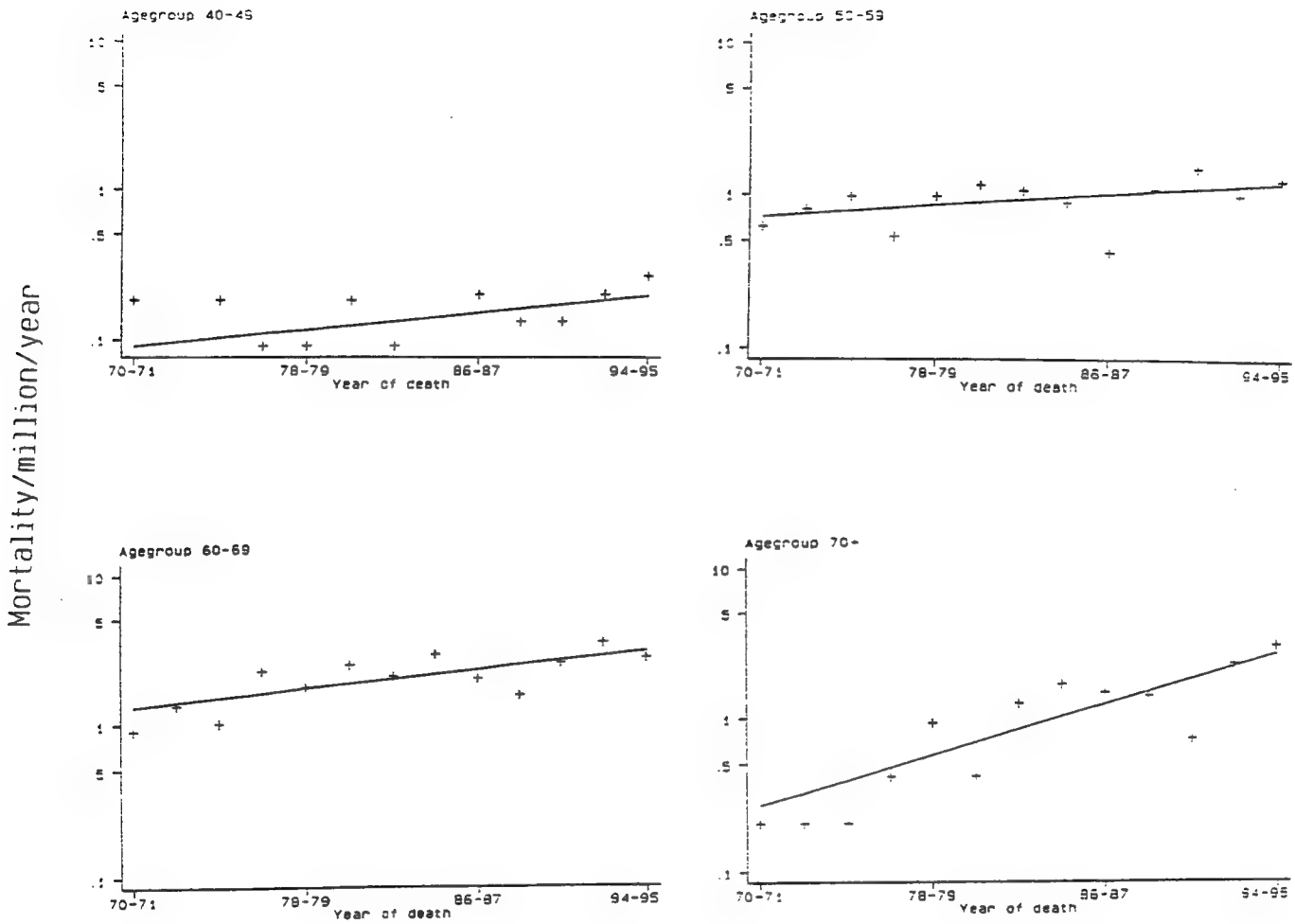


FIGURE 4 STANDARDISED MORTALITY RATIOS FOR SPORADIC CJD
ENGLAND AND WALES, 1970-1984

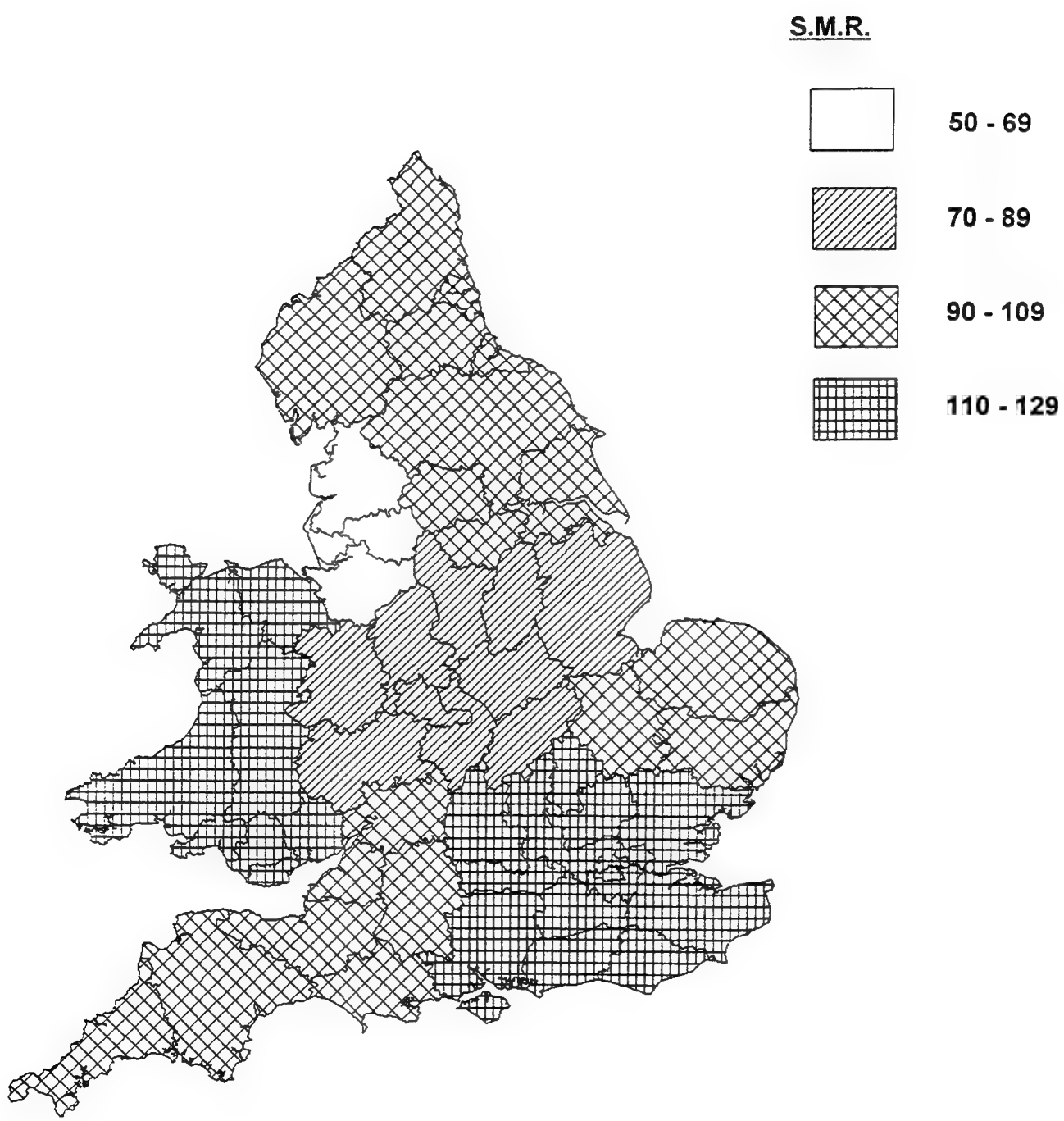


FIGURE 5 STANDARDISED MORTALITY RATIOS FOR SPORADIC CJD
GREAT BRITAIN, JANUARY 1985 - APRIL 1996

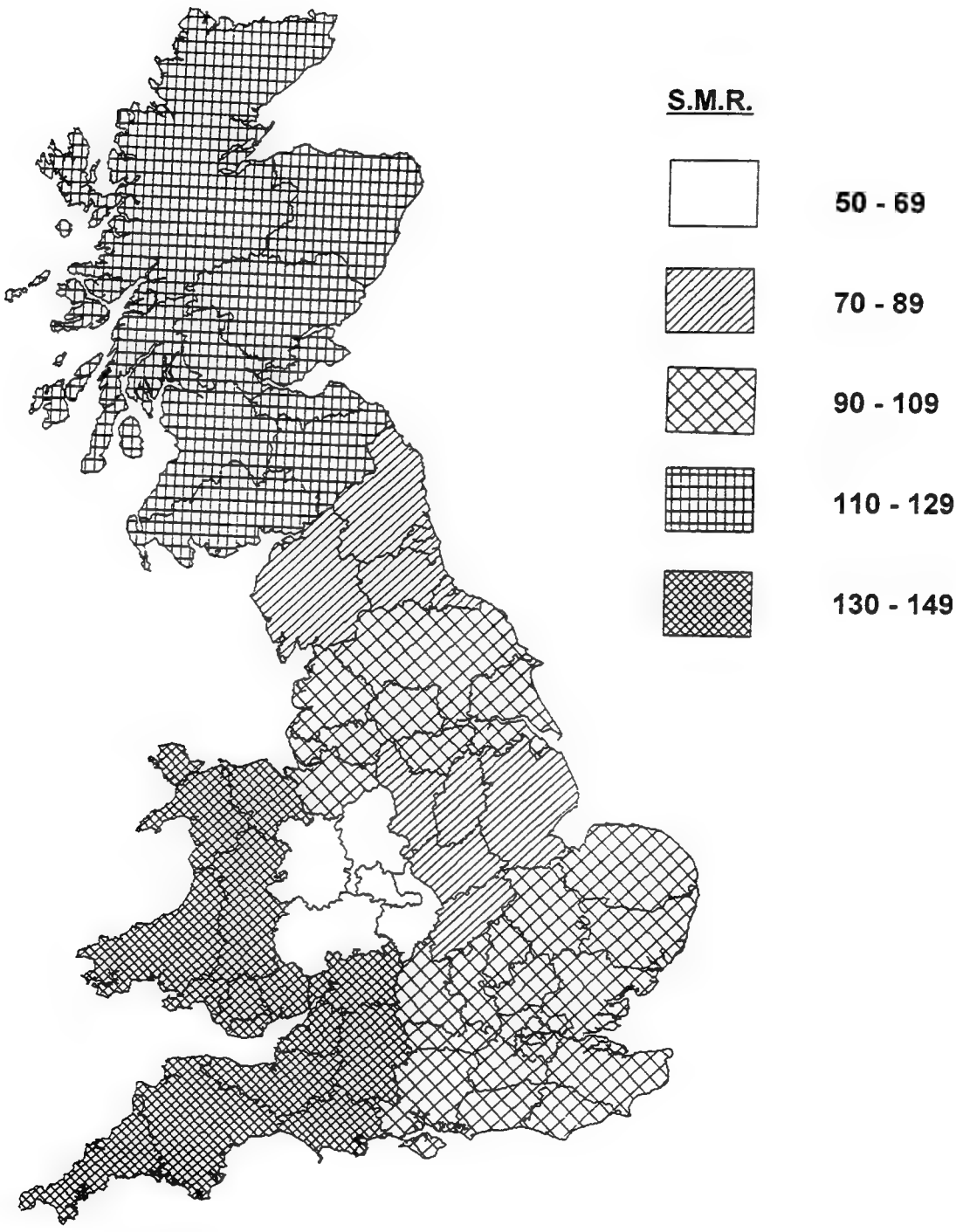


FIGURE 6

CREUTZFELDT-JAKOB DISEASE
AGE-SPECIFIC INCIDENCE RATES FOR AGE AT DEATH

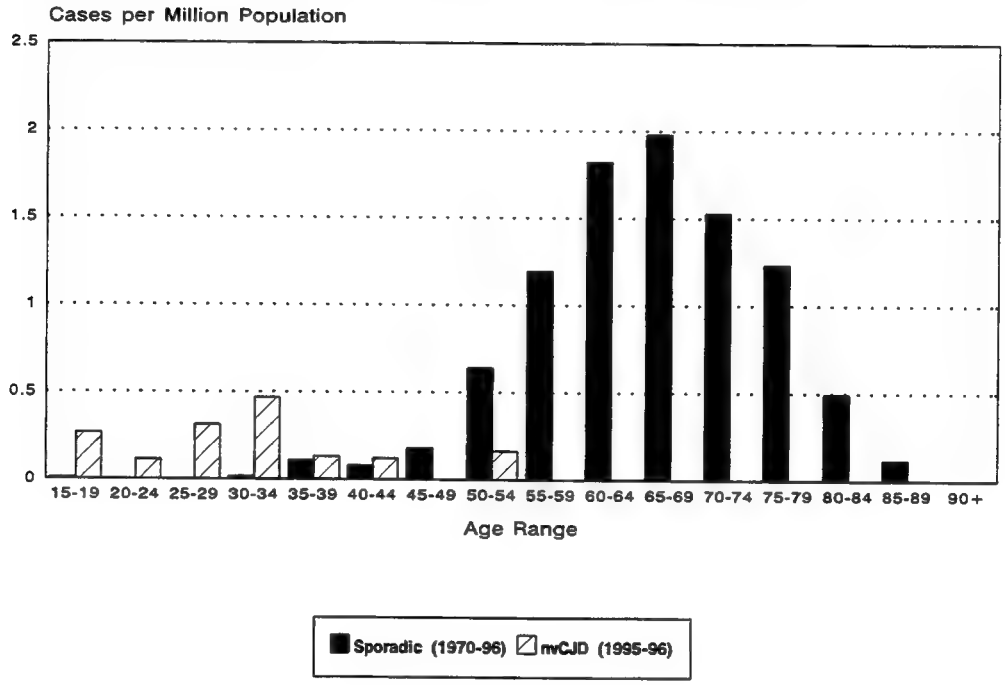


FIGURE 7 GEOGRAPHICAL DISTRIBUTION OF CJD IN THE UK
DEFINITE AND PROBABLE CASES (1 MAY 1990-30 APRIL 1996)

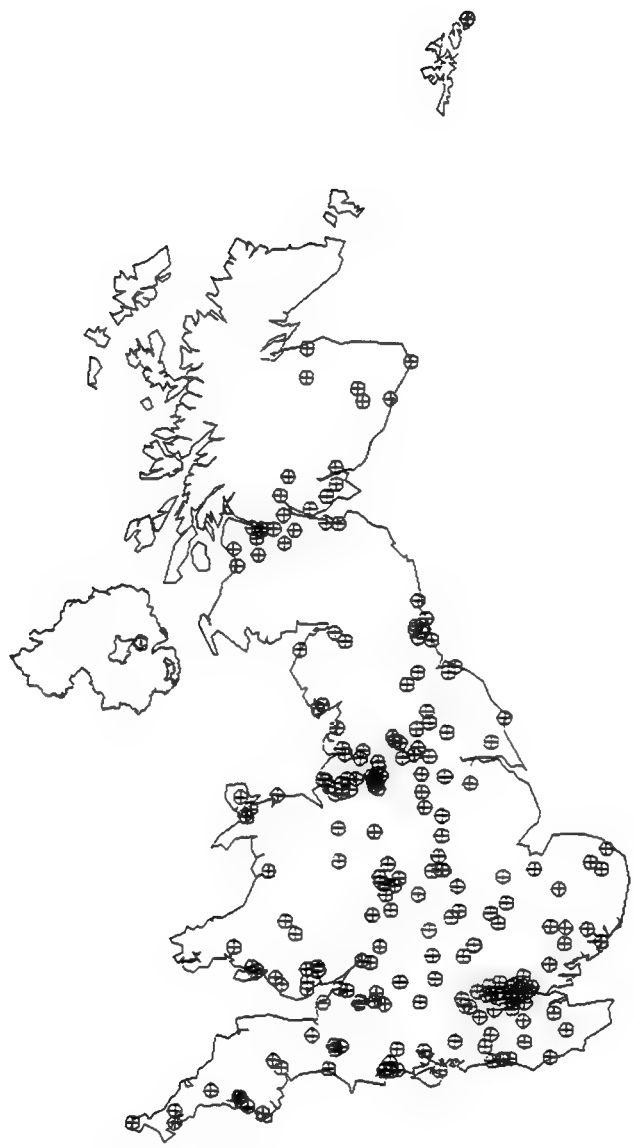
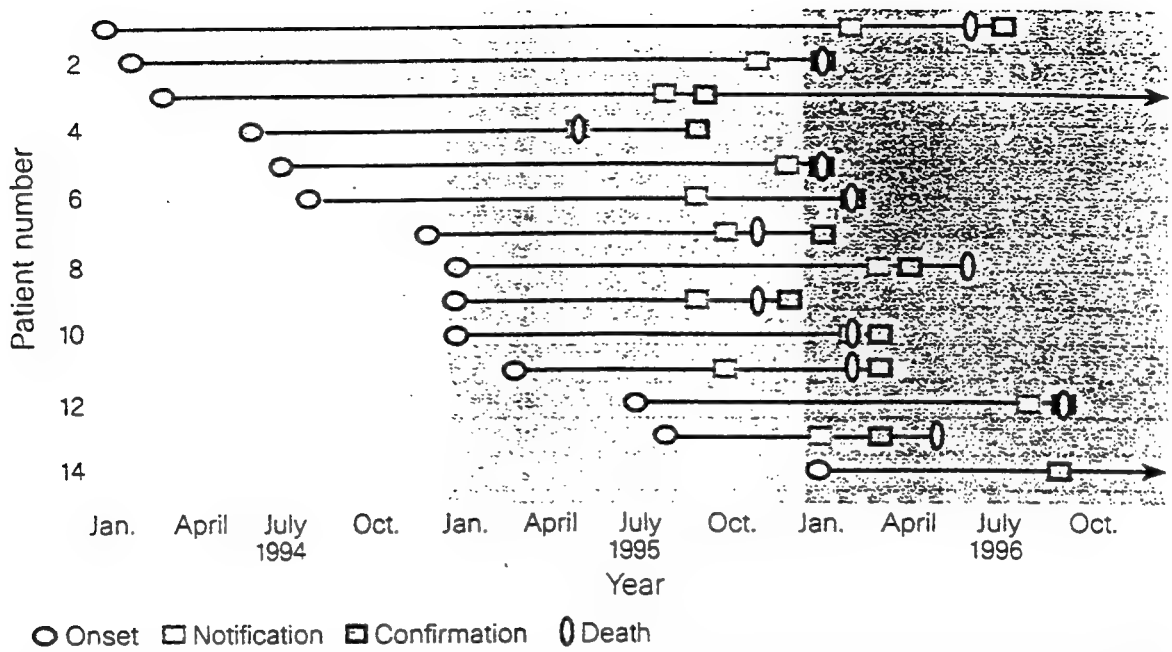


FIGURE 8



Dates of onset, death, referral and confirmation of diagnosis for 14 cases of new-variant CJD in the United Kingdom. For the case with most recent onset, referral and confirmation were almost simultaneous.

APPENDIX 1

DEPARTMENT OF HEALTH

Press release

97/158 Monday 7th July 1997

MONTHLY CREUTZFELDT-JAKOB FIGURES

The Department of Health is today issuing the latest monthly table, giving the numbers of deaths of definite and probable cases of Creutzfeldt-Jakob disease in the UK.

Year	Referrals	Deaths of definite and probable cases in the UK					
		Sporadic	Iatrogenic	Familial	GSS	nvCJD	Total
1985	-	28	1	1	0	-	28
1986	-	25	0	0	0	-	25
1987	-	23	0	0	1	-	24
1988	-	21	1	1	0	-	23
1989	-	28	2	2	0	-	32
1990	53	27	5	0	0	-	32
1991	75	32	1	3	0	-	36
1992	98	44	2	4	1	-	51
1993	78	36	4	2	2	-	46
1994	118	52	1	3	3	-	59
1995	86	34	4	2	3	3	46
1996	129	38	4	2	3	10	57
1997*	54	5	1	1	0	5	12

* To 31 May 1997. Plus one case of definite nvCJD still alive. Total number of definite and probable cases of nvCJD = 19.

NOTES FOR EDITORS

1. The next table will be published on 4 August 1997

Referrals: This is a simple count of all the cases which have been referred to the Unit for further investigation in the year in question. CJD may be no more than suspected; about half the cases referred in the past have turned out not to be CJD. Cases are notified to the Unit from a variety of sources including neurologists, neuropathologists, neurophysiologists, general physicians, psychiatrists, electroencephalogram (EEG) departments etc. As a safety net, death certificates coded under the specific rubrics 046.1 and 331.9 in the 9th ICD Revision are obtained from the Office for National Statistics in England and Wales, the General Register Office for Scotland and the General Register Office for Northern Ireland.

[MORE]

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Deaths: These columns show the number of deaths which have occurred in definite and probable cases of all types of CJD and GSS in the year shown. The figure includes both cases referred to the Unit for investigation while the patient was still alive and those where CJD was only discovered post mortem (including a few cases picked up by the Unit from death certificates). There is therefore no read across from these columns to the referrals column. The figures will be subject to retrospective adjustment as diagnoses are confirmed.

Definite and Probable: This refers to the diagnostic status of cases. In definite cases the diagnosis will have been pathologically confirmed, in most cases by post mortem examination of brain tissue (rarely it may be possible to establish a definite diagnosis by brain biopsy while the patient is still alive). Probable cases have not been confirmed pathologically; some cases are never confirmed pathologically because a post mortem examination does not take place (for instance where the relatives of the patient refuse consent) and these cases remain permanently in the probable category.

Sporadic: Classic CJD cases with typical EEG and brain pathology. Sporadic cases appear to occur spontaneously with no identifiable cause and account for 85% of all cases.

Probable sporadic: Cases with a history of rapidly progressive dementia, typical EEG and at least two of the following clinical features; myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs or akinetic mutism.

Iatrogenic: Where infection with CJD appears to have occurred accidentally as the result of a medical procedure. Most of the cases shown resulted from treatment with human growth hormone but others have occurred through contaminated neurosurgical instruments, dural grafts etc.

Familial: Cases occurring in families associated with mutations in the PrP gene (10 - 15% of cases).

GSS: Gerstmann-Straussler-Scheinker syndrome - an exceedingly rare inherited autosomal dominant disease, typified by chronic progressive ataxia and terminal dementia. The clinical duration is from 2 to 10 years, much longer than for CJD.

nvCJD: New variant CJD, the hitherto unrecognised variant of CJD discovered by the National CJD Surveillance Unit and reported in The Lancet on 6 April 1996. This is characterised clinically by a progressive neuropsychiatric disorder leading to ataxia, dementia and myeclonus (or chorea) without the typical EEG appearance of CJD. Neuropathology shows marked spongiform change and extensive florid plaques throughout the brain.

Definite nvCJD cases still alive: These will be cases where the diagnosis has been pathologically confirmed (by brain biopsy).

Probable nvCJD: Cases in which post-mortem (or brain biopsy) has not been carried out and which fulfil preliminary criteria for the clinical diagnosis of nvCJD. These criteria cannot yet be fully validated because of the limited experience of nvCJD.

[ENDS]

Section 6

Neuropathological Validation

Statement of Progress

The Neuropathology Laboratory in the CJD Surveillance Unit has continued to expand its activities both in terms of the number of cases studied and in complexity of the examinations performed. This increasing workload has been matched by an increase in the number of technical staff, and at present there are four technical staff working full-time in the laboratory to support the activities of the two neuropathologists (Dr J.W. Ironside and Dr J.E. Bell), with the database manager and secretary providing the essential backup for the smooth running of the laboratory. With the co-operation of colleagues in neuropathology and pathology across the UK a high post mortem rate and referral rate for suspected cases of CJD has been maintained.

Surveillance and Workload During 1995/96

A detailed breakdown of the workload of the laboratory is summarised in Table 20 for 1st May 1995-30 April 1996. The overall figures for suspected CJD cases from UK are the same as for the preceding year, but include 11 cases of the new variant form of CJD which have entailed a disproportionately large amount of effort into the examination and characterisation of the neuropathological features.

The neuropathological features of new variant CJD were characterised using the full resources of the laboratory for stereology, histochemistry, immunohistochemistry and image analysis (using equipment and personnel funded by BBSRC).

TABLE 20 **PERIOD 1st MAY 1995 - 30th APRIL 1996**

Total Number of Cases

Suspected Cases (UK)	
No evidence of CJD	9
Iatrogenic CJD (GHT)	5
GSS	3
FFI	0
CJD (classical)	23
nvCJD	11
Organic dementias	2
Alzheimers	8
Other*	4
Additional Investigations	
Animal	2
Historical	7
European Community	1
Rest of World	5
TOTAL CURRENT YEAR	**80**

* Ischaemia 2
Multiple infarcts 1
Congophilic angiopathy 1

The neuropathological features of nvCJD have been presented at meetings across the world, and material from these cases has been sent for review by all leading neuropathologists in the field of human transmissible spongiform encephalopathies across the world. It is accepted that this disorder constitutes a new form of human disease and that neuropathological examination is mandatory for a definite diagnosis (as stated by WHO). Prion protein immunocytochemistry is of major diagnostic value in these cases, particularly on brain biopsy specimens where only limited tissue is available for study and in which the full neuropathological spectrum of nvCJD is not readily apparent on routine histological preparations. Immunocytochemistry for prion protein is also provided as an investigative procedure to workers outside the UK who do not have the resources to undertake this investigation.

Brain Banking Activities

The laboratory houses a bank of frozen and fixed tissues from CJD cases (including nvCJD) and appropriate control cases. These are used extensively for research purposes both within the Unit and in collaboration with other leading centres in UK and across the world. In particular, material from nvCJD cases has been sent for investigation and transmission studies to Dr S. Prusiner (San Francisco), Professor J. Collinge (London), Dr F. Tagliavini (Milan), Professor H. Diringer (Berlin), Professor D. Dormont (Paris), Dr J. Hope and Dr M. Bruce (NPU, Edinburgh). The results of these investigations are awaited and are expected to provide additional significant information on the relationship of nvCJD to other human and animal transmissible spongiform encephalopathies, particularly BSE.

The running of the brain bank occupies an increasing amount of time for the technical staff and the database manager and incurs increasing costs for specimen transport on the consumables budget for the laboratory. The establishment of the brain bank was accompanied by reformulation of detailed protocols for specimen handling and transport; these protocols are now followed by many laboratories

across the world dealing with this material. The protocols are based on the guidelines established in UK by ACDP for whom Dr Ironside is a member of the Working Party on TSE.

Health and Safety

In addition to establishing protocols for tissue handling and transport, the neuropathology laboratory has established comprehensive protocols (based on ACDP guidelines) for all laboratory activities relating to CJD tissues. These protocols are in regular demand by centres across the world, and much time is spent by the technical staff providing advice and guidance to other centres involved in the handling of CJD tissues both as part of the diagnostic referral system and for research purposes.

The Unit also received numerous enquiries from other professional staff including nurses, infection control managers, undertakers and mortuary staff concerning issues related to clinical aspects of patients with CJD and arrangements for funeral and body viewing after autopsy. Dr Ironside has raised this as an area which could be usefully covered by the projected revision of the ACDP guidelines, as this is an area of increasing concern to those involved.

Laboratory Database

The appointment of a full-time database manager has allowed the computerisation of diagnostic laboratory records, facilitating case retrieval, analysis and research and providing up to date information on specimen categorisation and diagnosis.

The database will also be expanded to include workload data for each case, enabling a more accurate survey of laboratory output and facilitating a cost based analysis of laboratory activity.

Laboratory Visitors

A large number of visitors came to the laboratory in 1995/96 including neuropathologists, scientific research staff and MLSO staff. Major areas of interest for the visitors include protocols for safe specimen transport and handling, laboratory protocols and PrP immunocytochemistry.

Research Activities

Research activities in neuropathology are undertaken under the auspices of BBSRC, with a grant for the continued work of the computerised image analysis system established by Dr K. Sutherland. The use of this apparatus facilitated the early recognition of nvCJD, and has been increasingly used by both research staff and visiting students for studies of neuropathological phenotype in all forms of CJD in relation to clinical and genetic factors.

EU Projects

The neuropathology laboratory participates in two BIOMED projects: the surveillance project for CJD in the European Community (Dr R.G. Will) and the neuropathology project (Professor H. Budka). The CJD laboratory is a major participant in the neuropathology project, and took part in a trial of PrP immunocytochemistry which gained international recognition for the laboratory as the leading centre in this field. The laboratory has also provided diagnostic opinions on cases referred from EU and in turn provides material for teaching and research to Professor Budka's study.

External Meetings and Media Contacts

Dr Ironside and Dr Bell are invited with ever increasing frequency to talk on the neuropathology of CJD and related disorders at meetings across the UK and elsewhere in Europe and overseas. Priority is given in the UK to centres participating in the CJD surveillance project who have been involved in the investigation of a patient or who wish to undertake neuropathological investigations in CJD as a preliminary study for suspected cases. Increasing interest in CJD is also expressed from other medical and paramedical groups including microbiologists and virologists, infection control nurses and laboratory technical staff.

Section 7

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